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Melatonin treatment attenuates symptoms of acute nicotine withdrawal in humans

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Abstract

Nicotine withdrawlal is typically associated with negative changes in mood and performance, which often lead to relapse. We tested whether an oral 0.3-mg dose of melatonin administered 3.5 h after the nicotine withdrawal, and increasing circulating melatonin concentrations within the physiological range, affects the symptoms of acute 10-h (0800–1800 h) nicotine withdrawal in regular smokers. Self-reported ratings of mood, sleepiness, and cigarette craving were assessed hourly, using 17 visual analog scales (VAS). Computerized Four-Choice Reaction Time (FCRT) and Simple Auditory Reaction Time (SART) tests were used to assess performance every 2 h. Saliva samples were collected hourly, and salivary melatonin levels were measured using supersensitive radioimmunoassay. Compared with the placebo, melatonin treatment significantly reduced self-ratings of "anxious," "restless," "tense," "irritable," "angry," "depressed," "impatient," and "craving for cigarettes." Melatonin treatment did not significantly change the responses on the performance tests used. These data suggest that melatonin can help to counteract the acute effects of smoking cessation on mood.

Keywords: Nicotine withdrawal; Melatonin; Mood; Performance; Humans

1. Introduction

The attempt to quit smoking is associated with multiple symptoms of nicotine withdrawal, including anxiety, irritability, restlessness, increase in daytime sleepiness and nocturnal sleep disruption [11,13,19,22], which often lead to relapse. Pharmacotherapy of nicotine addiction is a promising field of research and clinical application [10]. Melatonin, a pineal hormone with a nocturnal pattern of secretion, is shown to affect multiple physiologic functions, including sleep promotion in humans and nonhuman primates (for review, see Refs. [20,28]). It is also reported that melatonin has an anxiolytic-like activity in rodents [1,2,7,8,16,18]. The idea of the present study was to conduct an investigation of whether melatonin treatment, using a dose that increases circulating melatonin concentrations within the physiological range, affects the symptoms of acute nicotine withdrawal in regular smokers.

2. Design and methods

A total of 12 subjects participated in the double-blind crossover placebo-controlled randomized trial. The subjects were recruited via an advertisement in a local newspaper, and included six males and six females, with an age range of 19–53 years, and a mean age (±SEM) of 27.9±3.8 years. Subjects reported that they smoked cigarettes for a period of 3–27 years, and had smoked at least 20 cigarettes a day in the past year. All of the subjects described several (two to five) unsuccessful attempts to quit smoking, during which they reported that they had experienced at least two of the following withdrawal symptoms: cigarette craving, increase in irritability, anxiety, daytime drowsiness, or nighttime sleep disturbances. Nine of the subjects were habitual coffee users, consuming two to four cups of coffee per day.

All of the volunteers participating in this study underwent a physical examination at the Massachusetts Institute of Technology (MIT) Clinical Research Center (CRC). Their urine and blood analyses, including complete blood count and comprehensive panel, were within the normal range. The subjects gave informed consent approved by the

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Committee on the Use of Humans as Experimental Subjects. Prior to the study, subjects participated in two training sessions to become comfortable with the computerized performance tests.

Subjects were admitted to the CRC on 2 consecutive days, at 0800 h. They were instructed to have a regular breakfast at home and were allowed to smoke two cigarettes and drink one cup of coffee before reporting to the CRC and were allowed to smoke ad lib in the evening, after leaving the CRC at 1830 h. Smoking or drinking caffeine-containing beverages was not allowed during the test sessions, and subjects' compliance was carefully controlled. Saliva samples were collected at 60-min intervals from 0900 to 1800 h, using Salivette tubes (Sarstedt, Newton, NC), to conduct further measurements of salivary melatonin levels.

Environmental illumination levels were held at 200 lx during both test days. During the test session, subjects were lying or sitting in bed but were allowed to walk to an adjacent bathroom. Lunch was served in bed at 1200 h, dinner was scheduled at the end of the test session at 1800 h.

At 1130 h, subjects ingested a gelatin capsule containing a 0.3-mg dose of melatonin (Nestle, Lausanne, Switzerland) mixed with microcrystalline cellulose "Avicel" (FMC, Philadelphia, PA) or microcellulose alone (placebo).

Self-reported ratings of mood, sleepiness and cigarette craving were assessed using 17 visual analog scales (VAS), with the following adjectives used: friendly, restless, down, anxious, sedated, headache, tense, depressed, angry, apathetic, irritable, feeling hungry, pleasant, difficulty concentrating, impatient, drowsy, craving for cigarettes. Each of the 17 VAS was a 120-mm line with the left-most point on the line representing 0=none at all, and the right-most point representing 120=extremely. The VAS score was measured as the distance in millimeter from the left end of the line by a research assistant "blind" to the order of drug administration.

Only eight subjects, who had previous extensive experience working with computers, were comfortable performing computerized performance tasks. Thus, the performance data analyzed was limited to that collected from eight subjects. These tasks were administered every 2 h on each test day. A short description of each follows.

Two computerized performance tests were used in this study.

2.1. Four-Choice Reaction Time (FCRT)

Subjects were presented with a series of visual stimuli at one of four adjacent spatial locations on a computer screen. The interstimulus interval was 300 ms. Subjects must correctly indicate the location of each stimulus by striking one of four corresponding adjacent keys on a microcomputer keyboard. A total of 400 trials were administered. The mean response latency and variance, as well as the number of true positive and true negative responses were registered and retained in a data file. The numbers of premature responses and time-out errors were also retained. Five warm-up stimuli and the responses were not included in the total number of trials presented.

2.2. Simple Auditory Reaction Time (SART)

In this task, the subject responded as rapidly as possible to the onset of an auditory signal. The test trials were presented in rapid succession following five warm-up trials. A 300-ms, 360-Hz tone warned the subject that a trial was about to begin. After a random delay of 100 to 900 ms, a 1000-Hz tone signaled the subject to respond. Subjects were instructed to respond as quickly as possible after the onset of the 1000-Hz tone. The subjects' response latency appeared on the computer screen for 300 ms between each trial. A warning message accompanied by an oscillating error tone occurred if the subject responds prematurely (prior to or within 50 ms of the onset of the stimulus tone) or failed to respond within 2000 ms. The subject must have acknowledged premature and time-out errors by pressing the Enter key. A 1000-ms delay occurred between error acknowledgment and the next trial to allow time for the subject to reposition his hand. The response latency and variance, as well as the number of premature and time-out errors, were retained in a data file. The task continued until 200 reaction times have been recorded.

Salivary melatonin concentrations were measured in 1-ml aliquots of saliva samples using a Buehlmann Laboratories radioimmunoassay (RIA) kit (ALPCO, Windham, NH) that employs the Kennaway G280 antibody. The extraction was conducted using C-18 columns. The limit of sensitivity of the melatonin assay is 0.5 pg/ml. Intra-assay coefficients of variation for control samples were 6.1% at 9 pg/ml and 6.3% at 22 pg/ml; the corresponding interassay coefficients of variation were 8.9% and 11.6%, respectively.

A two-factor repeated-measures ANOVA [treatment condition [2] × time of day [11] was performed on all the dependent measures (results of VAS scales and performance tests) to assess differences between placebo and melatonin treatment during a 10-h period of nicotine withdrawal. Significance was defined as $p < 0.05$. Mean values

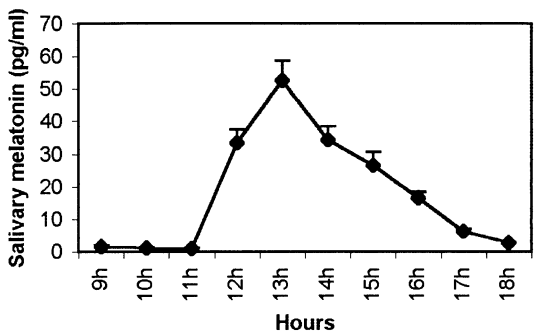

Fig. 1. Group mean (±SEM) salivary melatonin levels before and after melatonin treatment at 1130 h (n = 12).

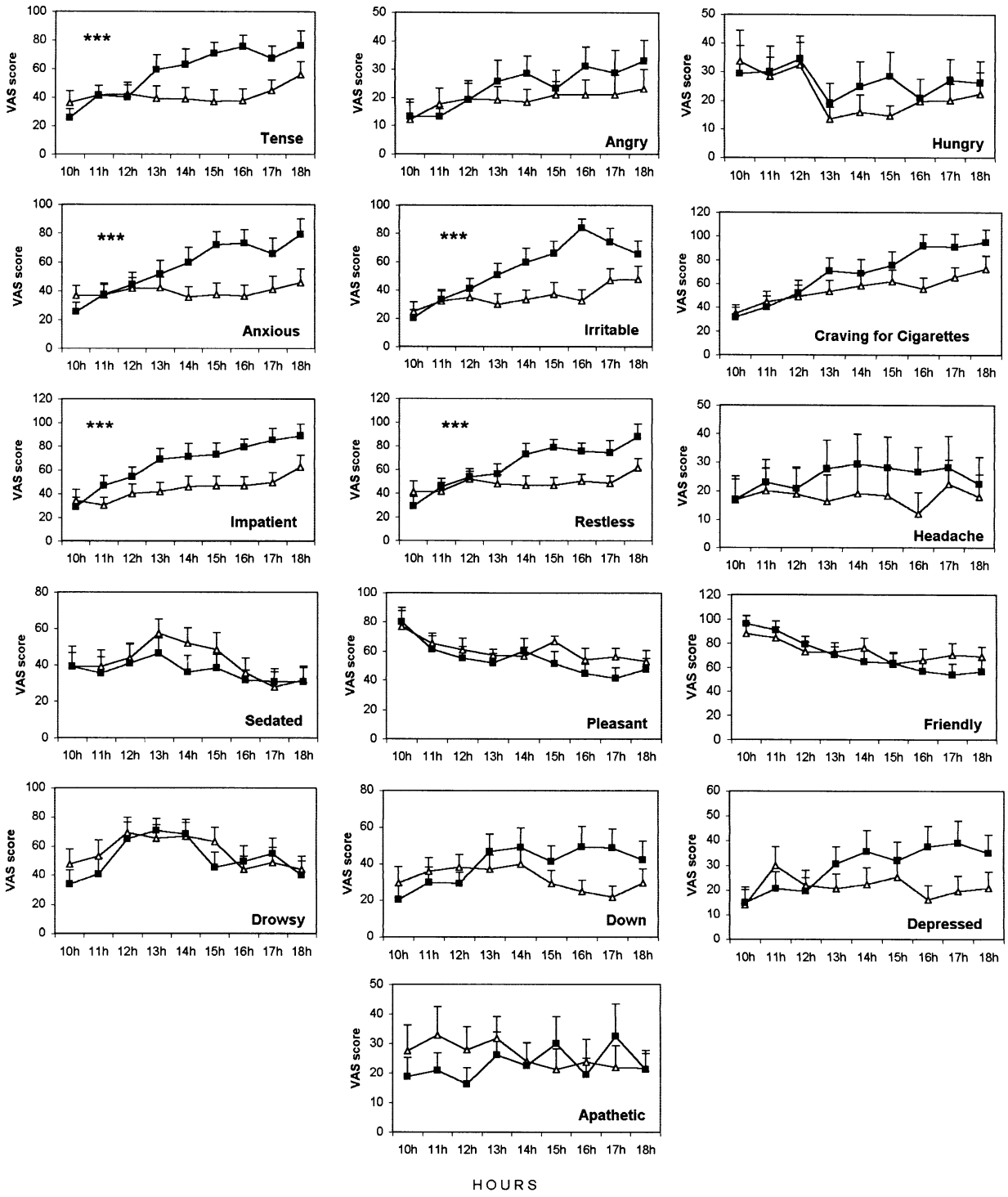

Fig. 2. Group mean (± SEM) VAS scores before and after administration of melatonin (triangle) or placebo (square) at 1130 h (n = 12).

(± SEM) are presented in the results. A relationship between the individual peak melatonin levels, or the individual area under the melatonin time–concentration curve for 6 h after the hormone ingestion, and changes in VAS scales or performance tests on the day of melatonin treatment were evaluated using Pearson's correlation coefficient.

3. Results

Salivary melatonin levels did not significantly change over time on the day of placebo treatment, and were within normal daytime levels for this hormone (1.4 ± 0.01 pg/ml). On the day when subjects received melatonin

treatment, a significant increase in the hormone levels was detected 30 min after the treatment (33.4 ± 3.1 pg/ml at 1200 h). Peak salivary melatonin levels were registered 90 min after the treatment, reaching 52.6 ± 4.2 pg/ml at noon, and continued to be significantly elevated compared to baseline until 1700 h (Fig. 1).

There was a marked individual variation in response to nicotine withdrawal. On the day when subjects received placebo treatment, there was a significant increase in group scores of restlessness, anxiety, tension, irritability, feeling down, impatience, and craving for cigarettes, and a decrease in pleasantness and friendliness during the 10-h period of nicotine withdrawal compared to baseline at 1000 h (Fig. 2). The severity of withdrawal symptoms did not correlate with the average number of cigarettes habitually smoked per day or habitual daily coffee intake. There were no significant differences between the pretreatment VAS scores on the days of placebo or melatonin administration. We found a significant effect of melatonin treatment on eight VAS scales (Fig. 2). Compared with the placebo, melatonin treatment significantly reduced self-ratings of "anxious." [$F(1,11) = 15.2$, $p < 0.01$]; "restless," [$F(1,11) = 6.4$, $p < 0.01$]; "tense," [$F(1,11) = 7.8$, $p < 0.05$]; "irritable," [$F(1,11) = 18.8$, $p = 0.001$]; "impatient," [$F(1,11) = 12.5$, $p < 0.01$]; "angry," [$F(1,11) = 26.3$, $p < 0.001$]; "depressed," [$F(1,11) = 5.7$, $p < 0.05$]; and "craving for cigarettes," [$F(1,11) = 4.9$, $p < 0.05$]. For most of these scales, there was also a significant treatment × time interaction: "anxious," [$F(9,99) = 4.1$, $p < 0.001$]; "restless," [$F(9,99 = 6.3$, $p < 0.0001$]; "tense," [$F(9,99) = 7.1$, $p < 0.0001$]; "irritable," [$F(9,99) = 4.5$, $p = 0.0001$]; "impatient," [$F(9,99) = 3.1$, $p < 0.005$]; "angry," [$F(9,99) = 1.8$, $p <$ NS], "depressed," [$F(9,99) = 3.7$, $p < 0.0005$], and "craving for cigarettes," [$F(9,99) = 5.4$, $p < 0.0001$]. Melatonin treatment did not significantly change self-ratings of "friendly," "feeling down," "sedated," "headache," "apathetic," hungry, "pleasant," "difficulty concentrating," and "drowsy." No significant changes in the responses on the performance tests used were documented. Significant order effects were found for response latency and the number of premature responses in FCRT, indicating that subjects' performance improved with practice.

No statistically significant correlation between the individual peak melatonin levels or the individual area under the melatonin time–concentration curve after melatonin ingestion and changes in self-reported ratings of mood, sleepiness, and cigarette craving or performance measured was found. The treatment-by-order interaction effects were non-significant for all measures.

4. Discussion

The major finding of this study is that melatonin treatment can reduce some of the symptoms of acute nicotine withdrawal. The group of smokers tested included individuals with extensive daily use of nicotine. All of these subjects reported a craving for cigarettes within 1–3 h after the last cigarette smoked. They also reported an increase in restlessness, anxiety, tension, irritability, feeling angry, feeling depressed, impatience, and feeling down during a 10-h period of nicotine abstinence while on placebo. A single low dose of melatonin administered approximately 3.5 h after the last cigarette was smoked, significantly reduced certain symptoms associated with smoking withdrawal, including restlessness, anxiety, tension, irritability, depression, impatience, feeling angry, and craving for cigarettes.

Smoking abstinence is typically associated with an increase in daytime sleepiness [4,11,12,15,19]. This may result from an acute cessation of availability of the potent psychostimulant nicotine and/or may be a side effect of chronic sleep deprivation because long-term tobacco abstinence disturbs the nocturnal sleep process [19]. In view of these facts and of melatonin's sleep-promoting effects, we were especially interested in any changes in reports of drowsiness and sedation in our subjects. There was a pronounced inter-individual variability in these parameters, with the group data not showing any significant effect of the treatment. The increase in subjective sleepiness observed in this study coincided with lunch time (1200 h), and could be substantially masked by a well-described daytime increase in subjective sleepiness.

Performance tests used in our study did not reveal differences in subjects' performance during the period of nicotine withdrawal or the effect of melatonin treatment compared to placebo. Some earlier studies reported changes in performance as a result of smoking cessation [13,21]; however, others did not find changes in performance on the psychomotor tasks [3,9]. It is important to note that all of our subjects who participated in performance testing were MIT students or trainees, and used computers on a daily basis. Their reaction times on the performance tests used were substantially lower than those listed for reference populations. Thus, lack of substantial changes in subjects' performance may be a result of their high skills that were not substantially impaired by increased anxiety or even light drowsiness.

Because subjects who participated in this study were deprived of caffeine, as well as nicotine, during the test sessions, caffeine withdrawal could contribute to changes in their emotional state. Although we did not see a correlation between the habitual coffee intake and the severity of withdrawal symptoms, melatonin may have the effect on caffeine withdrawal, which would be best studied in nonsmokers, i.e., independently of simultaneous nicotine withdrawal.

The oral dose of melatonin used in our study (0.3 mg) tends to induce circulating melatonin levels within the normal physiological range observed in young adults at night [5,31]. Salivary melatonin measurements using a supersensitive assay, such as used in this study, make it possible to accurately estimate circulating levels of the hormone [29] without causing subject's distress. Typically,

melatonin levels in saliva constitute approximately 20–30% of those in blood plasma or serum [14,17,29]. Thus, peak salivary melatonin levels observed in our subjects 90 min after the administration of the hormone would correspond to around 200 pg/ml in blood plasma. This would constitute a borderline level between high physiological and low pharmacological concentrations of the hormone. It is not known whether nicotine intake or cessation of smoking can disrupt melatonin secretion or metabolism in humans. However, in animal studies, nicotine administration is shown to inhibit melatonin synthesis [25] or cause phase shifts in the timing of the onset of melatonin production [6].

Sleep-promoting effects of physiologic doses of melatonin have been documented in healthy volunteers during the subjective day [5,24,30,31] and in insomniacs at night [27]. Thus, low doses of the pineal hormone might be a useful and safe alternative to other hypnotic medications for insomnia associated with nicotine withdrawal. The data presented in this article also indicates that melatonin can help to counteract the acute effects of smoking cessation on mood. While there are no clear contraindications to the use of physiologic doses of melatonin at night, the use of this "nocturnal" hormone during the day should be subject to certain limitations considering its potential hypnotic properties [26], ability to shift the phase of circadian rhythms [20] and possible negative effects on photoreceptors exposed to bright light [23].

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